Effects of a Long-Acting Somatostatin Analogue on Postprandial Hyperglycemia in Insulin-Dependent Diabetes Mellitus

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To determine whether an agent such as WY-41,747, a long-acting somatostatin analogue, could be useful as an adjunct to insulin in the treatment of diabetes mellitus, postprandial plasma glucose concentrations were determined in subjects with insulin-dependent diabetes rendered euglycemic with the Biostator insulin infusion device under four conditions: (1) subcutaneous minipump infusion of insulin alone (13 ± 1 units) over 30 minutes beginning 30 minutes before ingestion of a meal using insulin doses determined by the Biostator; (2) the same conditions as 1 but beginning immediately before meal ingestion; (3) the same conditions as 1 but with less insulin (7 ± 1 units) accompanied by the analogue (0.01–0.05 mg/kg); (4) the same conditions as 2 but with the analogue and less insulin (11 ± 1 units). Administration of the somatostatin analogue increased the effectiveness of insulin in controlling postprandial hyperglycemia and permitted satisfactory postprandial glycemic control when the insulin infusion was initiated immediately before meal ingestion. Administration of the analogue suppressed postprandial plasma glucagon and triglyceride concentrations and delayed xylose absorption. These results suggest that subcutaneous administration of a long-acting somatostatin analogue such as WY-41,747 along with insulin may be clinically useful in the treatment of diabetes mellitus.

THERE IS considerable evidence that the use of an agent such as somatostatin as an adjunct to insulin may be beneficial in the treatment of diabetes mellitus.[1-5] However, the short biologic half-life of somatostatin and its wide range of biologic actions[6] make the use of somatostatin itself impractical as a therapeutic agent. In order to circumvent some of these limitations, attempts have been made to produce analogues that are longer acting and more selective.[7,8] One of these analogues, Des-Ala^{1},Gly^{2}[His^{4,5},D-Trp^{8}]-somatostatin (WY-41,747), has been reported to be a potent and long-acting suppressor of glucagon and growth hormone secretion in animals.[9,10] Administration of this agent to streptozotocin-diabetic dogs decreased fasting plasma glucose levels and increased the effectiveness of insulin in controlling postprandial hyperglycemia.[10] The studies reported here were undertaken to evaluate the potential for use of this analogue as an adjunct to subcutaneously infused insulin in the management of human insulin-dependent diabetes mellitus.

MATERIALS AND METHODS

Informed written consent was obtained from seven male C-peptide deficient patients with insulin-dependent diabetes mellitus (aged 31 ± 3 years; known duration of diabetes 13 ± 2 years). All patients were within 20% of their ideal body weight based on Metropolitan Life Insurance Co tables.

The subjects were studied on five occasions separated by at least 1 week. The subjects were admitted to the outpatient facility of the Mayo Clinical Research Center between 7 and 8 AM in the postabsorptive state at least 24 hours after the last injection of intermediate-acting insulin. On all five occasions, the subjects were connected to a closed-loop intravenous insulin infusion device (Biostator, Life Science Instruments, Miles Laboratories, Elkhart, IN) and, after euglycemia had been established for at least two hours, they consumed over 20 minutes a standard meal (10 kcal/kg, 45% carbohydrate, 35% fat, 20% protein), which contained 5 g xylose for estimation of gastrointestinal absorption characteristics. On the first occasion, the amount of insulin given by the closed-loop device was used for estimation of subcutaneous insulin requirements for that meal as previously described.[11] On the subsequent four occasions, the insulin dosage thus derived was administered via a Miles-Mayo open-loop infusion device[11] as a 30-minute subcutaneous infusion of regular insulin (U100 pork, Eli Lilly and Co, Indianapolis, IN) in the abdominal wall beginning either 30 minutes before meal ingestion (protocols A and B) or immediately before meal ingestion (protocols C and D). The somatostatin analogue (WY-41,747, 0.01–0.05 mg/kg) was administered simultaneously with insulin in the abdominal wall (protocols B and D) as a separate subcutaneous infusion over 30 minutes using a Harvard pump. In protocols A–D, the patients remained connected to the Biostator for the total duration of each experiment, but the insulin infusion program was interrupted at the beginning of the meal. The dextrose infusion program was activated by the last hour of each experiment to deliver dextrose for blood glucose levels lower than 60 mg/dL. Seven age- and weight-matched nondiabetic volunteers (three men, four women) ingested identical meals and provided normal data for postprandial glucose, glucagon, and free insulin profiles.

Plasma glucose (YSI Glucose Analyzer, Yellow Springs Instrument Co, Yellow Springs, OH), plasma insulin (determined as free insulin using polyethylene glycol extraction of previously frozen samples),[12] plasma glucagon,[13] plasma growth hormone,[14] plasma xylose,[15] and plasma triglycerides[16] were measured at 15- to 30-minute intervals before and for five hours after meal ingestion. All data in the text and figures, unless otherwise indicated, represent the mean ± SEM and were evaluated for statistical significance using two-tailed paired *t* tests.[17]

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RESULTS

Plasma Glucose, Insulin, Glucagon, Growth Hormone, Triglycerides, and Xylose Concentrations when Insulin and WY-41,747 Were Administered 30 Minutes Before Meal Ingestion

Baseline plasma glucose (86 ± 3 *v* 93 ± 2 mg/dL), insulin (29 ± 2 *v* 32 ± 2 μU/mL), glucagon (141 ± 28 *v* 144 ± 25 pg/mL), growth hormone (2.9 ± 0.7 *v* 3.2 ± 0.6 ng/mL), and triglyceride (65 ± 5 *v* 55 ± 6 mg/dL) concentrations were comparable in the control (protocol A) and analogue (protocol B) experiments, respectively (Figs. 1 and 2, Table 1). The amount of insulin required for the standard meal as estimated from the insulin given by the closed-loop system was 13 ± 1 units. Following initiation of the insulin infusion in the control studies, the plasma insulin levels increased by 8 μU/mL over the 30-minute interval before meal ingestion, ($P < 0.05$); plasma glucose levels decreased to 81 ± 3 mg/dL (NS); plasma glucagon, growth hormone, and plasma triglyceride levels did not change. Over the same interval when less insulin (7 ± 1 *v* 13 ± 1 units, $P < 0.01$) was administered along with the somatostatin analogue, plasma insulin levels increased less than in the control studies (by 5 U/mL); plasma glucose levels decreased to 78 ± 3 mg/dL ($P < 0.01$); plasma glucagon levels decreased to 113 ± 22 pg/mL ($P < 0.01$), and the plasma growth hormone levels decreased to 1.8 ± 0.3 ng/mL ($P < 0.05$). Plasma triglycerides remained unchanged.

Following meal ingestion plasma glucose levels increased to a peak value of 155 ± 15 mg/dL at 100 minutes and returned to basal values by 180 minutes in the control experiments. Four of the six subjects subsequently developed sufficient hypoglycemia to activate the closed-loop device for the infusion of glucose. Plasma glucagon levels rose to a peak value of 230 ± 43 pg/mL at 80 minutes and did not return to basal values throughout the study. Plasma growth hormone levels decreased transiently, returning to basal values by 120 minutes. Plasma insulin levels increased to a peak value of 86 ± 13 μU/mL at 100 minutes and were still 52 ± 5 μU/mL at 300 minutes.

When less insulin was administered along with the somatostatin analogue, the plasma glucose levels initially decreased to a nadir of 58 ± 4 mg/dL at 40 minutes and gradually returned to basal values

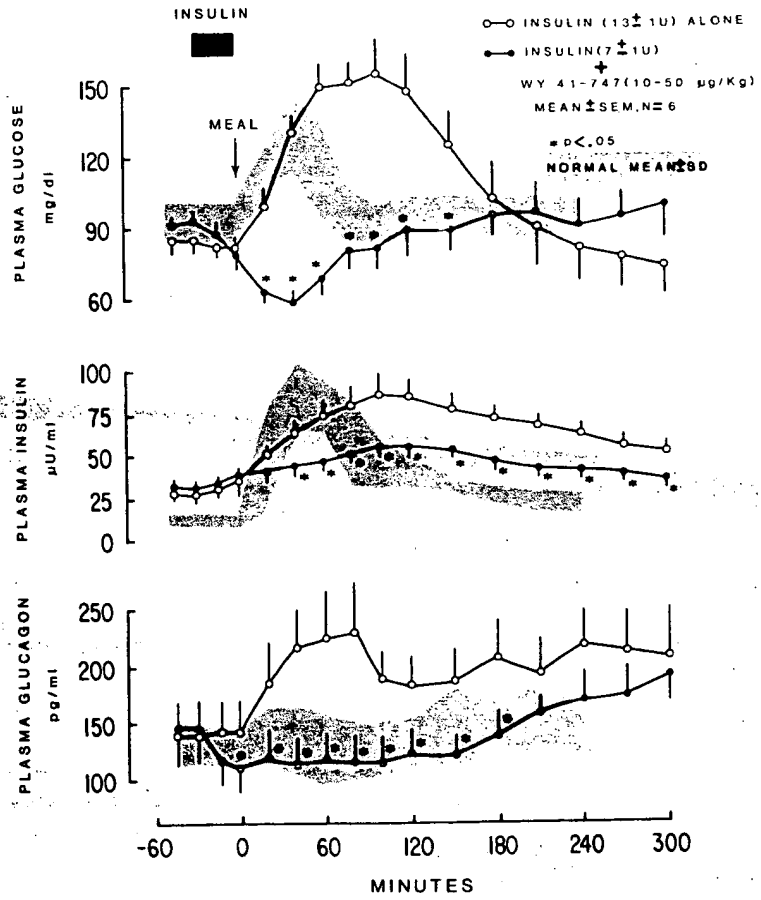

Fig. 1. Postprandial plasma glucose, insulin, and glucagon concentrations following a 30-minute subcutaneous infusion of insulin begun 30 minutes preprandially with and without concomitant administration of the somatostatin analogue (WY-41,747).

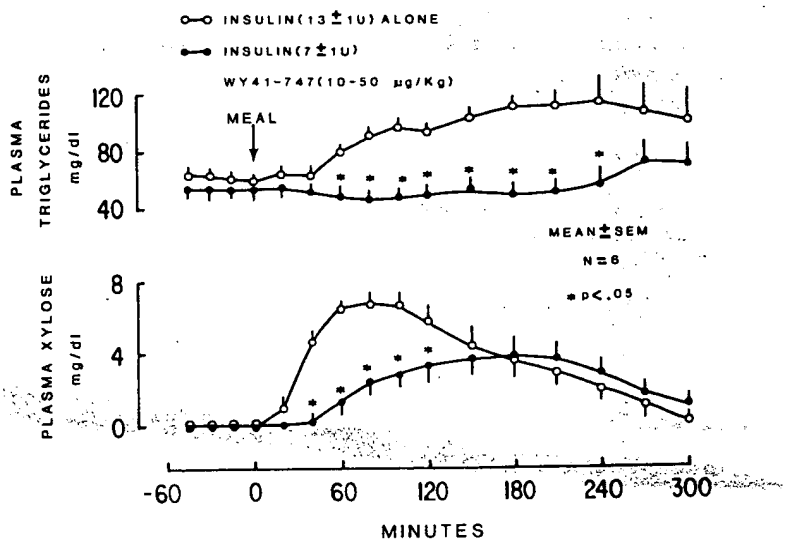

Fig. 2. Postprandial plasma triglyceride and xylose concentrations following a 30-minute subcutaneous infusion of insulin begun 30 minutes preprandially with and without concomitant administration of the somatostatin analogue (WY-41,747).

(99 ± 14 mg/dL) at 300 minutes. No subject developed symptomatic hypoglycemia. Plasma glucagon levels were significantly less than in the control experiments through 180 minutes, but plasma growth concentrations were not significantly different from those observed in control experiments. Both plasma xylose and plasma triglyceride levels increased significantly less than in the control experiments (Fig. 2).

Plasma Glucose, Insulin, Glucagon, Growth Hormone, Triglyceride, and Xylose Concentrations when Insulin and WY-41,747 were Administered Immediately Before Meal Ingestion

These experiments were undertaken to determine whether administration of the somatostatin analogue would permit satisfactory postprandial plasma glucose profiles to be achieved if insulin were administered immediately before meal ingestion. Baseline plasma glucose (89 ± 5 *v* 89 ± 3 mg/dL), insulin (28 ± 3 *v* 26 ± 4 µU/mL), glucagon (143 ± 27 *v* 140 ± 39 pg/mL), plasma growth hormone (3.5 ± 0.6 *v* 2.6 ± 0.7 ng/mL), and triglyceride (63 ± 6 *v* 57 ± 5 mg/dL) concentrations were comparable in the control (protocol C) and analogue (protocol D) experiments and were not significantly different from respective values in the studies in which insulin and the somatostatin analogue were administered 30 minutes before meal ingestion (Figs. 3, 4, Table 1). However, in contrast to observations in protocols A and B, these values did not change until meal ingestion.

Following meal ingestion in the control experiments, plasma glucose levels increased to a greater peak value

Table 1. Postprandial Plasma Growth Hormone Concentrations in Six Patients with Insulin-Dependent Diabetes Mellitus after Infusion of Insulin With and Without Concomitant Infusion of the Somatostatin Analogue WY-41,747

Plasma Growth Hormone Level (ng/mL) at min	Protocol			
	Insulin Alone at −30 min	Insulin + WY-41,747 at −30 min	Insulin Alone at 0 min	Insulin + WY-41,747 at 0 min
−45	2.8 ± 0.6	3.2 ± 0.7	—	—
−30	2.5 ± 0.6	3.3 ± 0.6	4.3 ± 1.0	2.7 ± 0.9
−15	3.4 ± 1.0	2.7 ± 0.3	3.4 ± 0.8	2.9 ± 1.0
0	2.9 ± 0.6	1.8 ± 0.3	3.0 ± 0.8	2.1 ± 0.3
20	2.7 ± 0.6	1.6 ± 0.2	2.3 ± 0.2	1.6 ± 0.3
40	2.1 ± 0.3	1.4 ± 0.3	1.5 ± 0.1	1.5 ± 0.2
60	1.8 ± 0.2	1.2 ± 0.2	1.7 ± 0.4	1.8 ± 0.3
80	1.9 ± 0.3	1.3 ± 0.2	1.6 ± 0.2	1.4 ± 0.2
100	1.6 ± 0.3	1.6 ± 0.2	1.5 ± 0.3	1.5 ± 0.3
120	2.9 ± 1.0	1.9 ± 0.5	1.6 ± 0.3	1.4 ± 0.3
150	3.9 ± 1.0	1.4 ± 0.2	2.6 ± 1.0	1.6 ± 0.2
180	4.2 ± 1.0	1.6 ± 0.4	2.4 ± 0.7	2.4 ± 0.6
210	3.3 ± 0.7	2.3 ± 0.4	2.3 ± 0.4	2.2 ± 0.4
240	4.1 ± 0.9	2.2 ± 0.4	3.4 ± 1.7	12 ± 7.0
270	3.8 ± 0.8	3.1 ± 0.6	2.3 ± 0.7	15 ± 10.0
300	3.3 ± 0.4	3.9 ± 0.6	2.4 ± 0.5	8 ± 2.0

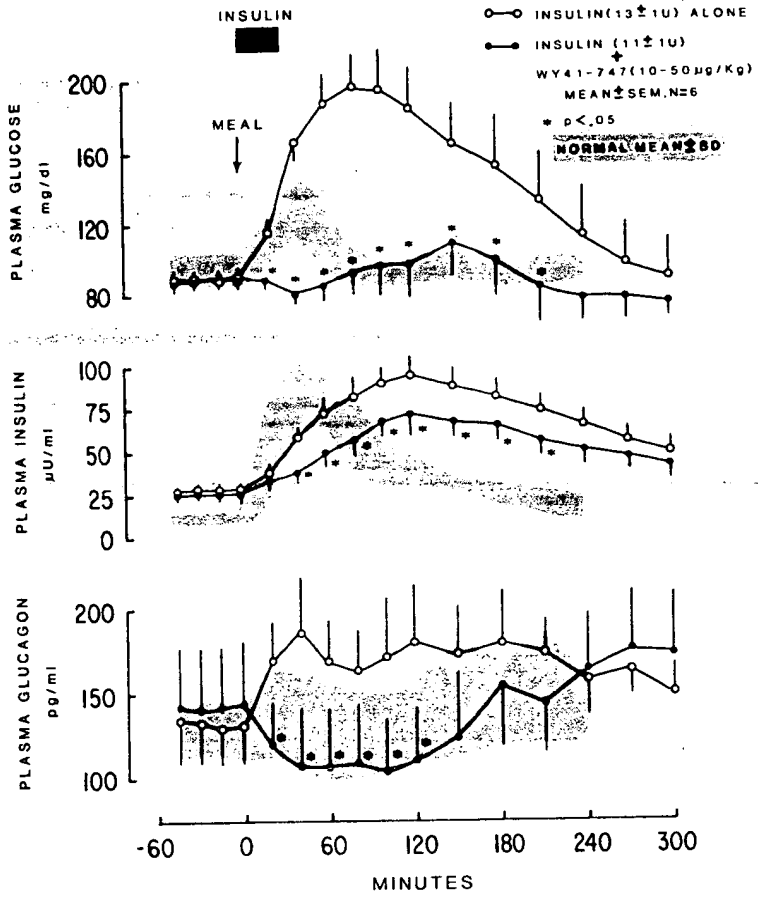

Fig. 3. Postprandial plasma glucose, insulin, and glucagon concentrations following a 30-minute subcutaneous infusion of insulin begun immediately before meal ingestion with and without concomitant administration of the somatostatin analogue (WY-41,747).

(196 ± 18 mg/dL) than was observed when insulin alone was given 30 minutes before meal ingestion and did not return to basal values until 240 minutes. Plasma glucagon levels increased to a peak value of 209 ± 46 pg/mL and returned to baseline values by the end of the study. Plasma insulin levels increased to a peak value of 95 ± 9 µU/mL at 120 minutes and were still 51 ± 8 µU/mL at the end of the study. Plasma growth hormone levels decreased transiently, returning to baseline values by 150 minutes. Following meal ingestion, when less insulin (11 ± 1 *v* 13 ± 1 units) was given along with the somatostatin analogue, plasma

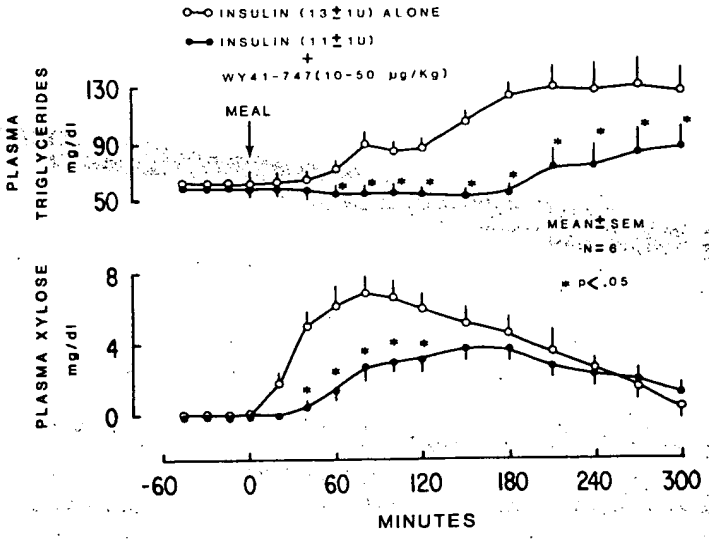

Fig. 4. Postprandial plasma triglyceride and xylose concentrations following a 30-minute subcutaneous infusion of insulin begun immediately before meal ingestion with and without concomitant administration of the somatostatin analogue (WY-41,747).

glucose levels did not increase significantly and were markedly less than values observed in control experiments over the same interval. Plasma glucagon levels decreased to a nadir of 102 ± 31 pg/mL ($p < 0.01$) and remained lower than values observed in the control experiments for 120 minutes, but plasma growth hormone values were not significantly different from those observed in control experiments. Both plasma xylose and plasma triglyceride levels increased significantly less than in the control experiments (Fig. 4).

Adverse Effects

No serious adverse effects were noted. In all three experiments in which the analogue was administered at a dose of 0.05 mg/kg, mild to moderate nausea and epigastric discomfort lasting less than 10 minutes occurred. In two of six experiments and in one of three experiments in which the analogue was administered in doses of 0.025 and 0.01 mg/kg, respectively, slight transient nausea or epigastric discomfort also occurred. In only one of the twelve control experiments was transient nausea observed.

DISCUSSION

The present studies demonstrate that the administration of des-Ala^1,Gly^2[His^{4,5},D-Trp^8]-somatostatin analogue (WY-41,747) significantly enhanced the effectiveness of subcutaneously administered insulin in limiting the postprandial hyperglycemia of insulin-dependent diabetes. Moreover, administration of the analogue along with insulin permitted satisfactory control of postprandial hyperglycemia when the subcutaneous insulin infusion was initiated immediately before meal ingestion.

The injection of the analogue suppressed plasma glucagon concentrations for two to three hours and, as evidenced by decreased postprandial plasma xylose and triglyceride values, also apparently delayed meal absorption by one to two hours. Both suppression of postprandial plasma glucagon levels and the delay in the absorption of the meal could have been responsible for the increased effectiveness of insulin in controlling postprandial hyperglycemia.[6] Since plasma growth hormone was comparably suppressed after administration of insulin alone and insulin plus the somatostatin analogue, it appears unlikely that changes in the secretion of growth hormone contributed to the improvement in postprandial hyperglycemia under the present short-term experimental conditions.

Inappropriate hyperglucagonemia in response to a meal is a common feature of human diabetes and is thought by some to aggravate postprandial glucose intolerance by decreasing the clearance of the ingested glucose by the liver.[18-20] Following subcutaneous injection or infusion of insulin either 30 minutes before a meal or at the beginning of meal ingestion, systemic plasma insulin levels increase slowly and remain elevated for several hours.[21] Thus, in the patients with insulin-dependent diabetes, postprandial portal venous insulin levels are probably subnormal initially; this could lead to decreased uptake of the ingested glucose by the liver. On the other hand, the sustained hyperinsulinemia observed in the late postabsorptive period could lead to late hypoglycemia.[11] Indeed, four of our subjects required dextrose infusions at the end of the five-hour experimental period when insulin alone was administered 30 minutes before the meal. Plasma free-insulin concentrations at that time were still greater than baseline levels. This late hyperinsulinemia is probably a consequence of both the dose of insulin that is usually required for near-normal meal disposal when the nonphysiologic subcutaneous route is employed[22] and the decreased clearance of insulin because of the presence of anti-insulin antibodies.[23]

Plasma glucose levels decreased transiently following the beginning of meal ingestion when insulin plus the analogue were administered 30 minutes before the meal. Moreover, four subjects required dextrose infusions towards the end of the experiment in which infusion of insulin plus the analogue was initiated at the beginning of meal ingestion. In both of the above occasions, less insulin had been administered than in the control experiments. Thus, it is likely that even less insulin might have been used since postprandial plasma glucose concentrations over the five-hour period of these experiments were lower in the diabetic subjects than in nondiabetic volunteers (101 ± 3 mg/dL) when insulin plus the analogue were injected 30 minutes before meal ingestion (84 ± 11 mg/dL, $P < 0.05$) or at the beginning of the meal (89 ± 11 mg/dL, $P < 0.05$).

Postprandial plasma triglyceride concentrations were decreased following administration of the analogue in the present studies. Somatostatin itself has a similar effect on postprandial plasma triglyceride levels; this could be due to decreased splanchnic blood flow,[24] biliary and pancreatic secretion,[25,26] gastrointestinal motility[27] or decreased intestinal absorption.[28] Whether a degree of malabsorption was superimposed on the slower absorption of the ingested meal following analogue administration cannot be concluded from the present short-term experiments. However, no subject had diarrhea, and in experiments in dogs treated with WY-41,747 no evidence for malabsorption was found.[10]

In summary, the present studies demonstrate that

subcutaneous administration of a long-acting somatostatin analogue along with subcutaneous infusion of insulin increases the efficacy of insulin in controlling postprandial hyperglycemia in patients with insulin-dependent diabetes mellitus. The analogue was well tolerated and permitted satisfactory control of postprandial hyperglycemia when insulin was administered at the time of meal ingestion. Such an agent may prove useful as an adjunct to insulin in the management of diabetes mellitus.

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